Updates In Management Of Membranous Nephropathy

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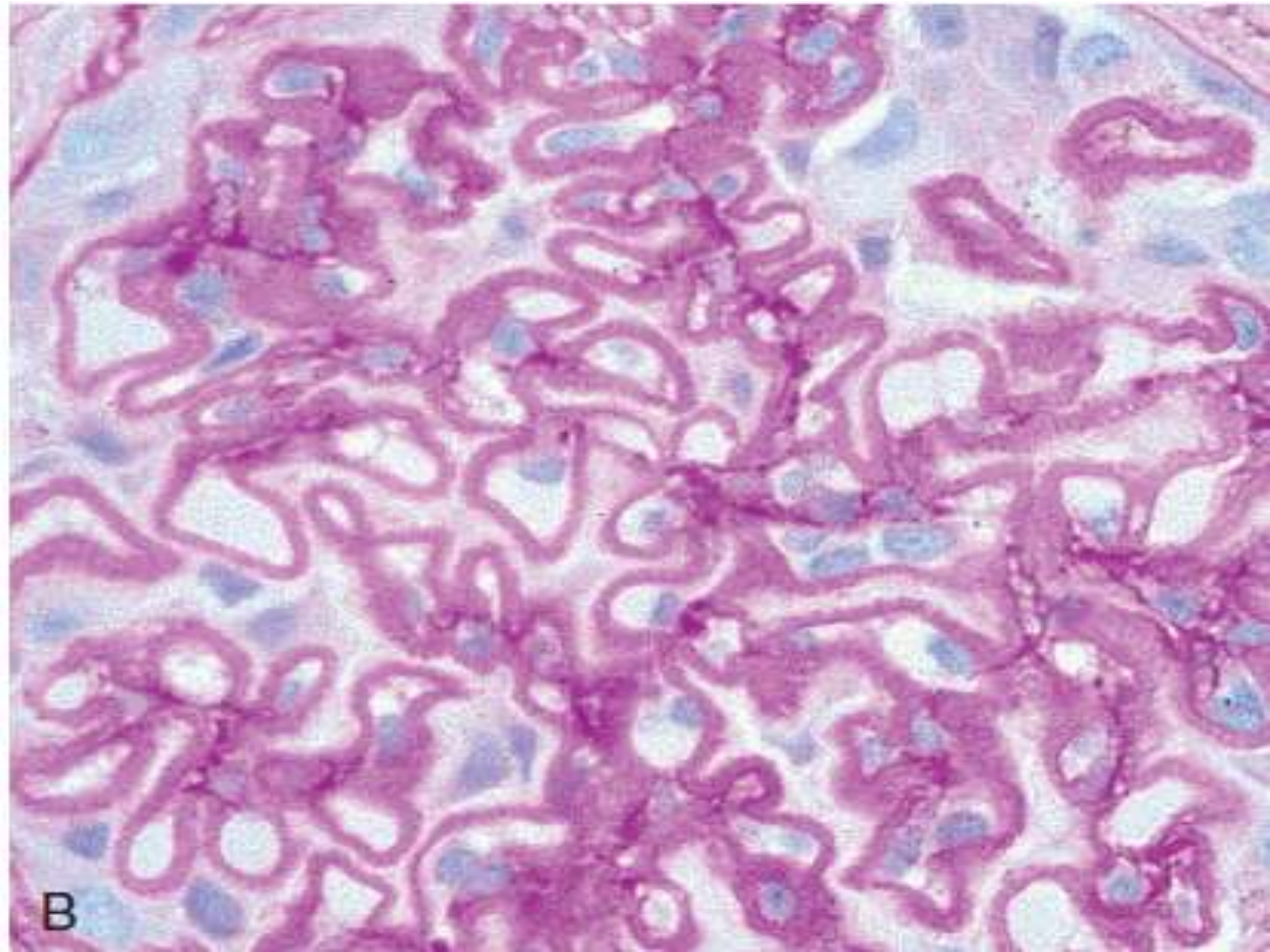
- Membranous nephropathy (MN) is an immune complex glomerular disease in which immune deposits of IgG and complement components develop predominantly or exclusively beneath podocytes on the subepithelial surface of the glomerular capillary wall.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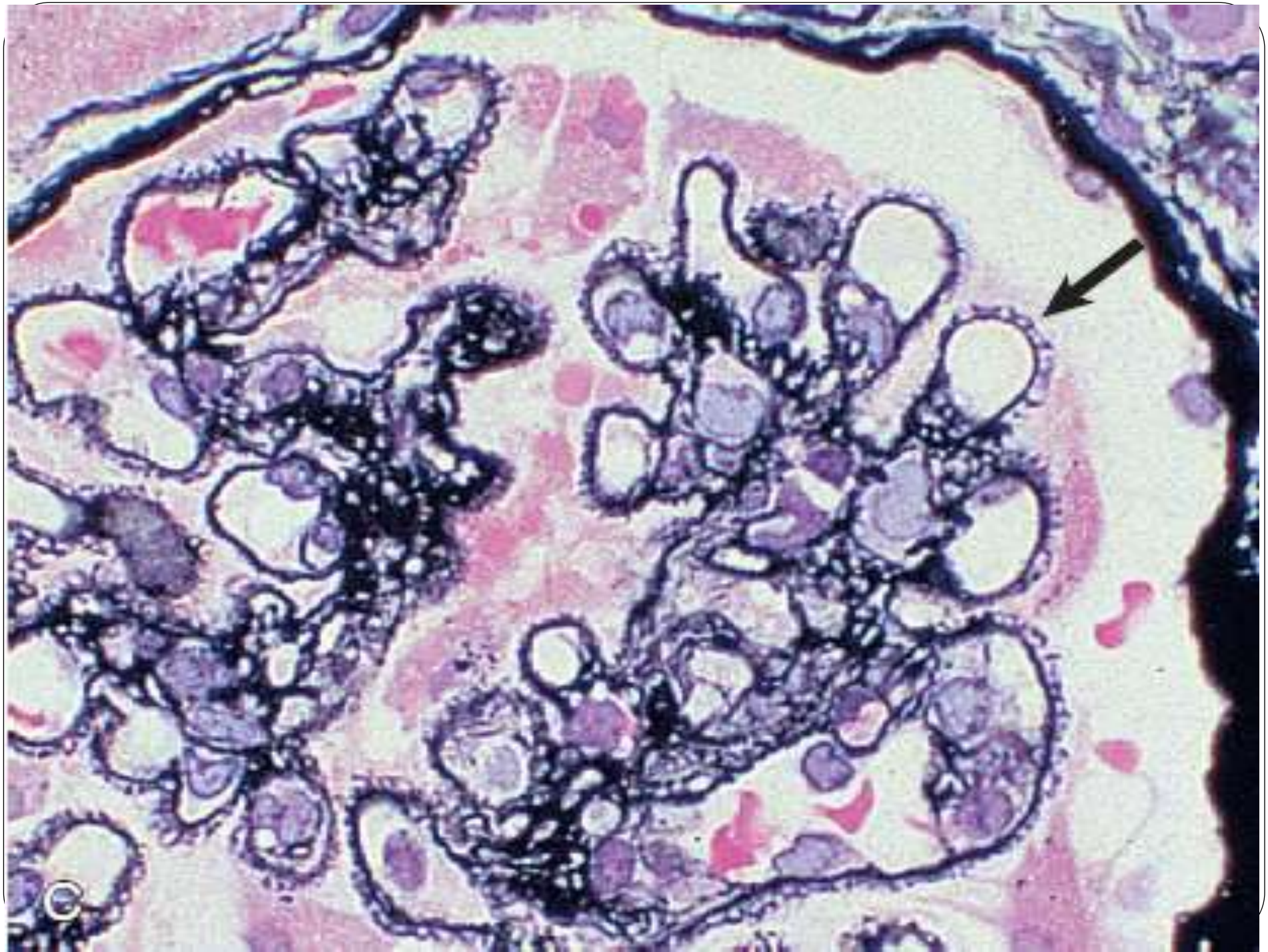

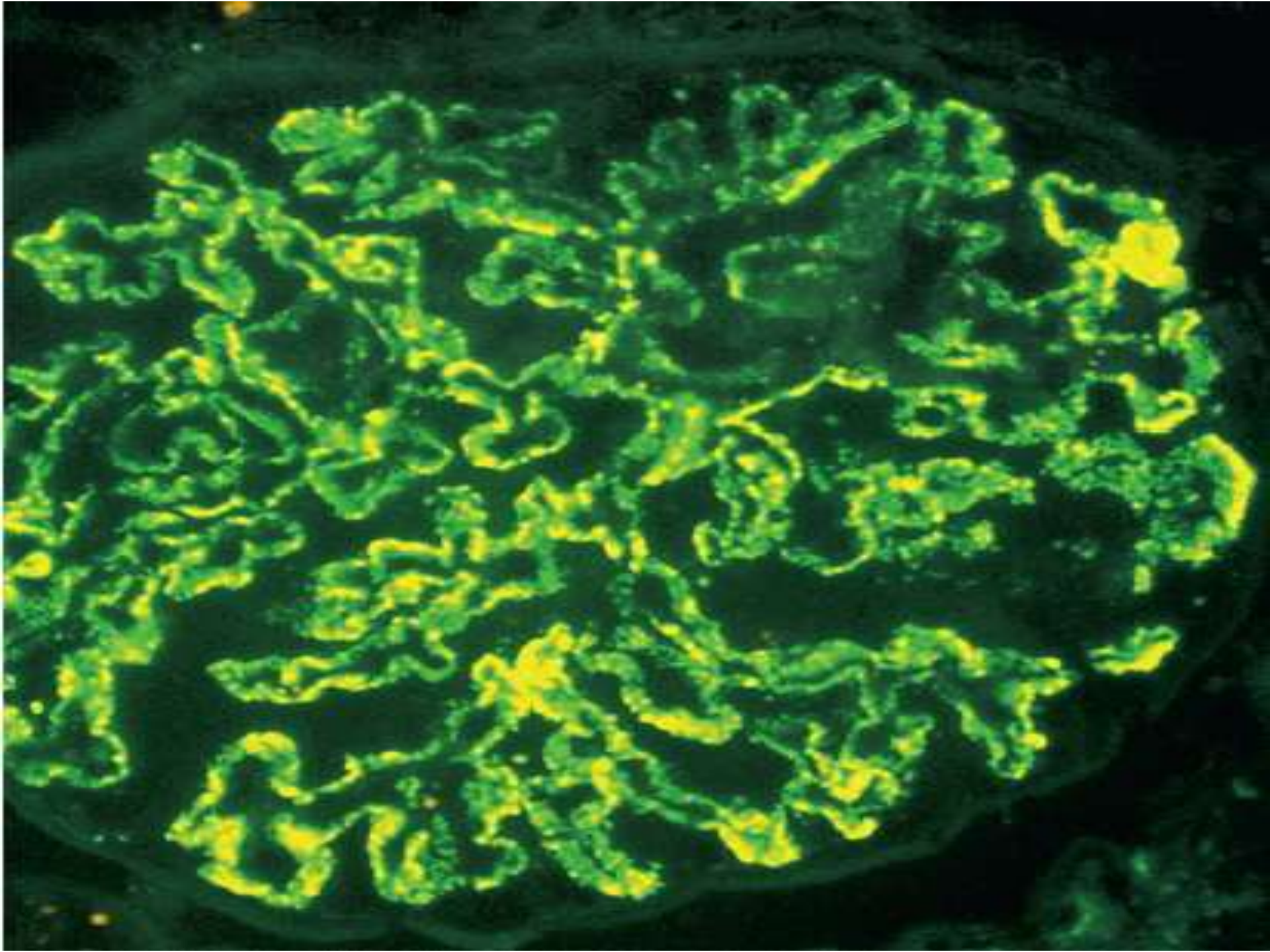

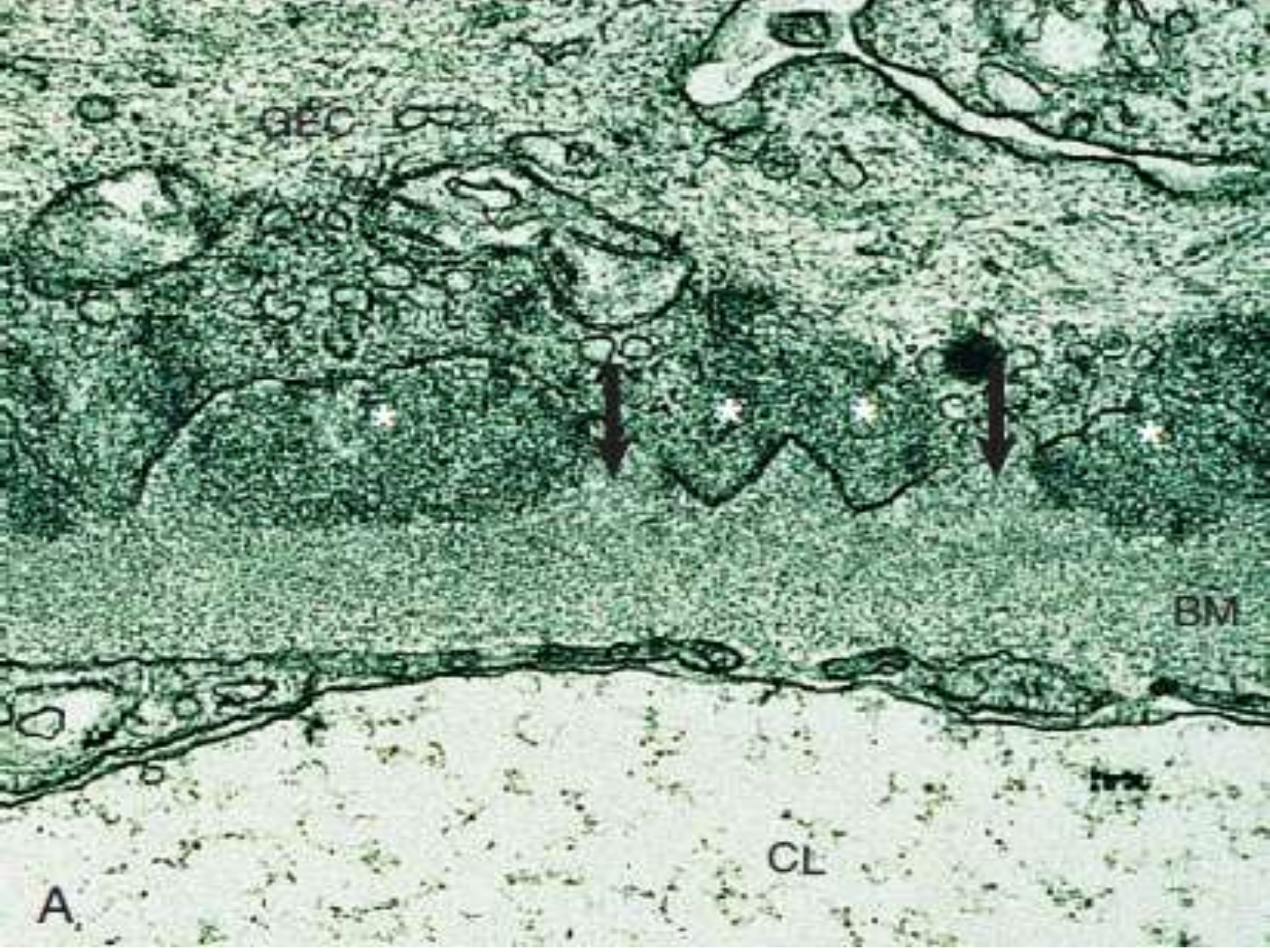
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In about 75% to 80% of patients, MN occurs in the absence of any identifiable cause or initiating event and is known as *idiopathic or primary MN.*

Classification and Causes of Membranous Nephropathy

Primary		
Anti-PLA_2R associated (70%-80%) Idiopathic (20%-30%)		
Secondary	**Common**	**Uncommon**
Autoimmune diseases	Class V lupus nephritis	Rheumatoid arthritis Autoimmune thyroid disease IgG4-related systemic disease Anti-GBM and ANCA-associated crescentic glomerulonephritis
Infections	Hepatitis B	Hepatitis C virus (HCV) Human immunodeficiency virus (HIV) Syphilis Schistosomiasis
Malignancy	Solid tumors (colon, stomach, lung, prostate)	Non-Hodgkin lymphoma Chronic lymphocytic leukemia (CLL) Melanoma
Drugs or toxins	Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 (COX-2) inhibitors	Mercury-containing compounds Gold salts D-Penicillamine, bucillamine
Miscellaneous		Sarcoidosis Anticationic bovine serum albumin
Alloimmune		
Graft-versus-host disease following hematopoietic stem cell transplantation *De novo* membranous nephropathy in renal allograft Fetomaternal alloimmunization to neutral endopeptidase		

Distinguishing Histopathologic Features of Primary Versus Secondary Membranous Nephropathy

Primary	Secondary
Immunofluorescence Microscopy	
IgG4 > IgG1, IgG3	IgG1, IgG3 > IgG4
IgA, IgM absent	IgA, IgM may be present.
Mesangial Ig staining absent	Mesangial Ig staining may be present.
C1q negative or weak	C1q positive
PLA_2R positive and co-localizes with IgG	PLA_2R negative
Electron Microscopy	
Subepithelial deposits only ± mesangial deposits rarely	Subepithelial deposits ± mesangial and subendothelial deposits

Clinical Features of Membranous Nephropathy

Rare in children: less than 5% of total cases of nephrotic syndrome

Common in adults: 15% to 50% of total cases of nephrotic syndrome, depending on age; increasing frequency after 40

Males > females in all adults groups

Caucasians > Asians > African Americans > Hispanics

Nephrotic syndrome in 60% to 70%

Normal or mildly elevated blood pressure at presentation

"Benign" urinary sediment

Nonselective proteinuria

Tendency to thromboembolic disease*

Other features of secondary causes: infection, drugs, neoplasia, systemic lupus erythematosus

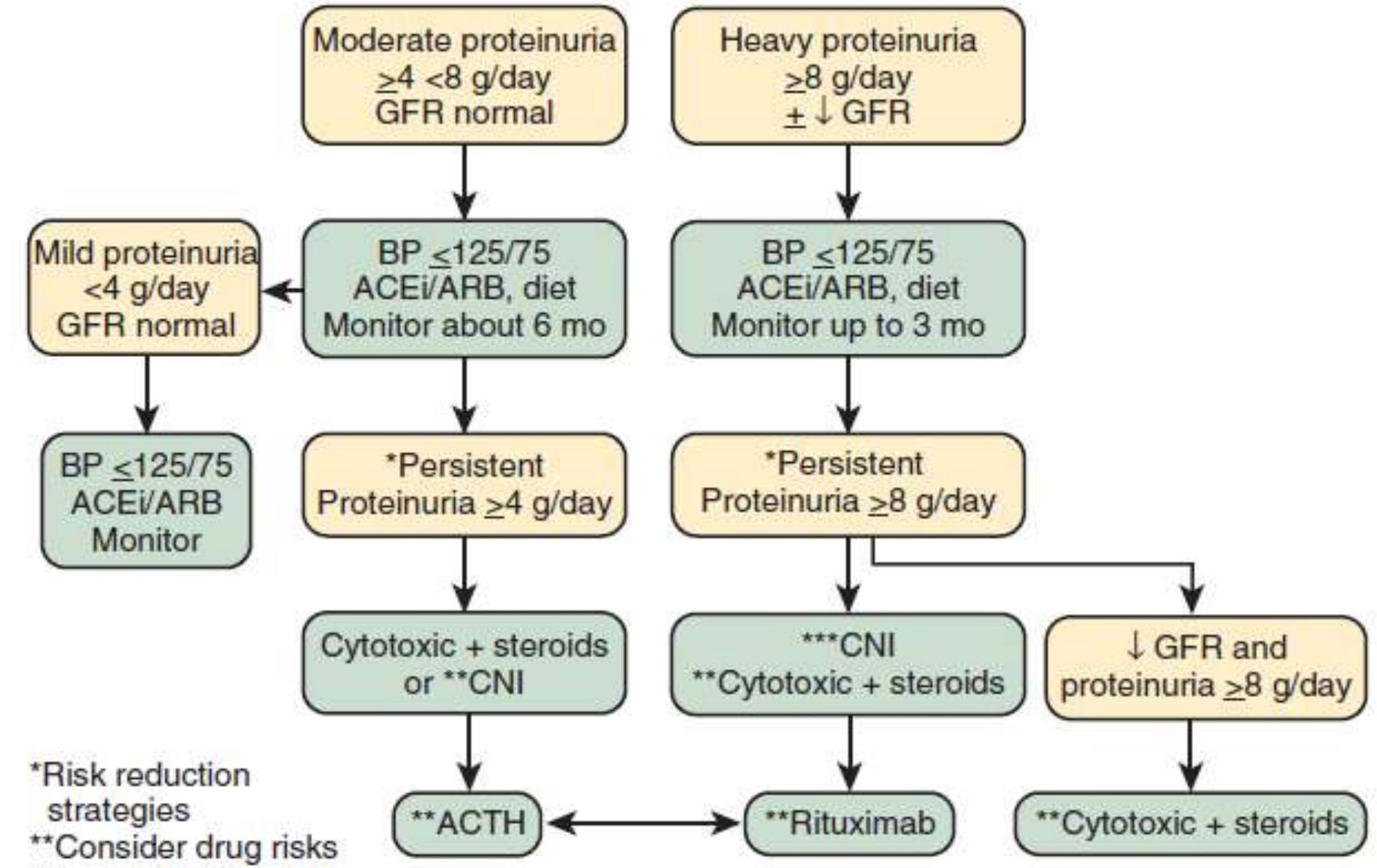
- patients presenting with less than 3.5 g/day of proteinuria, no RBC casts, no hypertension, normal renal function, and no systemic features suggestive of a secondary cause have a relatively benign prognosis.

- One of the best models to calculate risk of MN takes into consideration the initial creatinine clearance, the slope of the creatinine clearance during a fixed period, and the lowest level of proteinuria during that observation period.

Renal Disease Risk Categories		
Low Risk	**Medium Risk**	**High Risk**
Normal serum creatinine and creatinine clearance plus proteinuria <4 g/day over 6 months of observation	Normal or near-normal creatinine clearance and persistent proteinuria >4 g/day to <8 g/day over 6 months despite maximum conservative treatment	Deteriorating renal function and/or persistent proteinuria >8 g/day for 3 (up to 6) months of observation

Risk categories of renal disease progression in membranous nephropathy

MN Treatment Algorithm



The use of oral corticosteroids as a single agent for the treatment of MN is not recommended.

- Studies using mycophenolate mofetil (MMF) in MN patients report conflicting results. However, even in the most optimistic study, although initial response was high (used in combination with prednisone), the relapse rate within months approached 50%.

- The role of MMF in the treatment of MN is currently uncertain.

Rituximab

- Rituximab is a murine/human chimeric anti-CD20 mAb that depletes B cells and was licensed in 1997 for the treatment of non-Hodgkin's lymphoma.
- A subsequent expansion of interest in rituximab as an immunomodulatory agent resulted in a label for rheumatoid arthritis in 2006 and preliminary reports of efficacy across the spectrum of autoimmune disease.
- More than 20 studies of almost 300 patients reported response rates averaging 75% in refractory lupus or lupus nephritis treated with rituximab.
- Responses are accompanied by falls in anti– double-stranded DNA antibodies, correction of complement depletion, and reduction in glucocorticoid requirement.

Table 1. Rituximab studies[a]

Study	Concomitant Treatments	Remission (Nephritis)	Serology Change[b]	Relapse
ANCA vasculitis				
Keogh et al. (2005)[18]	GC, PLEX	10/11 CR, 1/11 PR (4/4)	8/11 negative all decreased	2 (7, 12 mo)
Keogh et al. (2006)[25]	GC	10/10 CR (7/7)	6/10 negative all decreased	1 (9 mo)
Smith et al. (2006)[20]	GC, MMF	9/11 CR, 1/11 PR (6/6)	6/10 negative all decreased	6/10 (median 16.5 mo)
Stasi et al. (2006)[19]	GC	9/10 CR, 1/10 PR (6/6)	8/10 negative all decreased	3/10 (12, 16, 24 mo)
SLE				
Looney et al. (2004)[22]	GC, AZA, MTX, HCQ	13/18 CR or PR (4/6)	No significant change	4/11 (timing NR)
Gottenberg et al. (2005)[33]	NR	7/13 CR, 2/13 PR (2/4)	Variable	2/9 (9, 15 mo)
Sfikakis et al. (2005)[34]	GC	5/10 CR, 3/10 PR (8/10)	Decrease	3/8 (5, 5, 8 mo)
Smith et al. (2006)[20]	MMF, AZA GC	6/11 CR, 5/11 PR (6/6)	No significant change	7/11 (median 12 mo)
Vigna-Perez et al. (2006)[35]	GC, MMF, MTX, AZA	18/22 improved, 5/22 CR (12/22)	No significant change	NR
Nwobi et al. (2008)[36]	GC, MMF HCQ	7/18 CR, 10/18 PR (17/18)	Decrease	5/18
Podolskaya et al. (2008)[16]	GC, CYC AZA, MMF, HCQ	11/19 CR, 8/19 PR (15/15)	Decrease	NR
Ng et al. (2007)[14]	GC, CYC, HCQ	30/32 CR or PR (21/21)	Decrease	18/32 (mean 10 mo)
Lindholm et al. (2008)[15]	GC, CYC MTX, MMF	30/33 CR or PR (11/17)	Decrease	11/30
Membranous glomerulonephritis				
Fervenza et al. (2008)[11]	ACE/ARB	8/14 response	–	NR
Ruggenenti et al. (2006)[21]	ACE/ARB	14/23 response	–	2/9

[a]Clinical studies of rituximab in primary or secondary glomerulonephritis involving at least 10 patients. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AZA, azathioprine; CR, complete remission; CYC, cyclophosphamide; GC, glucocorticoids; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MTX, methotrexate; NR, not reported; PLEX, plasma exchange; PR, partial remission.

[b]ANCA for ANCA vasculitis; anti-dsDNA for systemic lupus erythematosus (SLE).

- A near universal finding has been the achievement of peripheral B cell (CD19 or CD20 lymphocytes) depletion below 1 10^6/L after rituximab, and failure to achieve depletion is correlated with poor or no clinical response.
- B cell recovery is detectable after 6 to 9 mo, and although prolonged B cell depletion is associated with a prolonged clinical response, B cell return is not closely associated with disease activity, and relapses have occurred before B cells return.

- Polymorphisms in the FcRIII receptor influence rituximab-induced B cell lysis and associate with incomplete B cell depletion with low-dosage rituximab .

- The development of antichimeric antibodies to rituximab (HACA) is found in up to 30% of treated patients; although in the majority of cases they seem to have no clinical effect .

Retuximab And MN

- Most of the reported experiences with rituximab are from uncontrolled pilot trials or case series from two centers in Bergamo, Italy, and the Mayo Clinic in the United States.
- The following treatment protocols have been tried for IMN : four weekly doses of 375 mg/m2, which is standard dosing for treatment of lymphoma; two 1000-mg doses given biweekly, which is standard for rheumatoid arthritis; and a B cell–driven protocol in which dosing is titrated to the number of circulating B cells.
- Among nephrotic patients with IMN, the four-dose lymphoma and two-dose arthritis regimens seem to have similar efficacy despite faster B cell recovery after the two-dose regimen. no detectable differences in the progressive reduction of anti-PLA2R levels between the two dosing regimens

- A recent study by Ruggenenti et al. [2012] looked at 100 patients treated with rituximab for idiopathic MN. 27% of the patients had a complete and 38% a partial remission of the nephrotic syndrome.
- The authors feel this may be a first line agent for some patients.
- However, this was not a randomized controlled trial.

- Regardless of the regimen administered, proteinuria tends to decline slowly and remissions may occur up to 2 years after treatment.
- Interestingly, Beck et al. 2011, showed that after administration of rituximab, the median time to reach undetectable anti-PLA2R levels was 9 months (range, 1–18 months).

- This may explain the delay in remissions, because the reduction in antibody levels seems to precede the decline in proteinuria by months.

- It is interesting to note that remissions continue to occur well after the end of therapy with rituximab or alkylating agents; complete remissions can be seen12 months after the completion of these interventions. This is in contrast to what is observed after cyclosporine or tacrolimus, in which typically no additional remissions occur once treatment stops.

- Relapse rates after rituximab therapy are difficult to estimate given the limited longitudinal data.
- There are two published studies (n=31) that followed patients for up to 24 months and relapses were infrequent (6% and 13%, respectively).
- Currently, there are no established guidelines regarding the issue of retreatment and investigators have taken different approaches.
- Empirical redosing, B-level, protienuria, PLA2R .

Toxicity

- Although acute infusion reactions are often mild and manageable (e.g., fever, chills, pruritus, and skin rash), more severe and potentially fatal reactions (e.g., acute respiratory distress syndrome, bronchospasm, angioedema, shock and myocardial infarction) as well as potentially fatal mucocutaneous reactions (e.g., Stevens–Johnson syndrome and toxic epidermal necrolysis) can occur.
- Rare cases of the devastating demyelinating central nervous system disease, progressive multifocal leukoencephalopathy, have also been reported, although typically when administered as part of multidrug immunosuppressive regimens.
- Finally, the long-term safety profile of rituximab in glomerular diseases is largely unknown, particularly if repeated courses are needed.

- Controlled prospective trials are needed to compare the efficacy and toxicity of rituximab with CNIs and cytotoxic drugs.
- More data are needed to clarify the role of rituximab in patients with impaired or declining renal function and the effects of rituximab on hard endpoints such as dialysis and death.

ACTH

- Although listed as a new therapy for glomerular diseases, the natural pituitary hormone ACTH has been FDA-approved for treatment of the nephrotic syndrome since the 1950s.
- Its resurgence has come as a result of the successful use in Europe of synthetic ACTH, in treating the nephrotic syndrome,Berg Al.2004.
- In some such studies, several patients with FSGS had dramatic decreases in proteinuria after treatment with ACTH.
- In subsequent publications some patients resistant to other therapies have responded well to natural ACTH treatment Bomback AS et al,2011,2012.

- A small multicenter randomized control trial of 32 patients by Ponticelli et al.2006 compared efficacy of 6 months of alkylating agents alternating with corticosteroids to tetracosactrin intramuscular injections for 1 year (1 mg twice weekly).
- There were no significant differences in cumulative remission rates between the treatment arms ,initially (93% versus 87%, respectively) or at final follow-up of 21 months (75% total versus 87%, respectively).
- However, it is notable that these patients were treatment naïve, with preserved kidney function and low to modest degrees of proteinuria (5–6 g/d)—all of which may lead to an overly optimistic view of remission rates

- Outcomes were not as favorable in a recent prospective study from the Netherlands in which tetracosactrin was administered to high-risk IMN patients (Hofstra j,et al 2011).
- After 9 months of treatment, only 44% of patients achieved remission and relapse rates were high (43%).
- Other investigators have reported similarly high relapse rates after drug discontinuation, particularly after short courses of therapy.

- A different formulation of ACTH, a natural highly purified gel, is available in the United States (corticotropin; Questcor Pharmaceuticals Inc, Anaheim Hills, CA).
- In a retrospective study of corticotropin in proteinuric glomerular diseases, 9 of 11 (82%) patients with IMN achieved a remission (three complete; six partial).
- Interpretations of the data are limited due to the uncontrolled nature of the study, the variable dosing regimens used, a possible carry-over effect from previously administered immunosuppression, and short follow-up

- The mechanisms by which ACTH exerts its antiproteinuric effect are not understood.

- The effects are not thought to be mediated by induction of endogenous cortisol from the adrenal glands because administration of corticosteroids as monotherapy has not been effective in IMN.

- recently, attention has focused on a possible direct effect of ACTH on podocytes as expression of one of the natural receptors for endogenous ACTH (melanocortin receptor-1) has been identified in human kidney tissue, mainly in the podocyte ,lindskog A et al 2010.

- In support of this theory, experimental evidence in a rat model of membranous disease showed that treatment with an agonist of the melanocortin receptor-1 reduced proteinuria and improved podocyte morphology compared with untreated rats.

Treatment of nephrotic syndrome with adrenocorticotropic hormone (ACTH) gel

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Purpose: A synthetic adrenocorticotropin (ACTH) analog has shown efficacy in Europe as primary and secondary therapy for nephrotic syndrome, but there is no published experience using the natural, highly purified ACTH gel formulation, available in the United States, for nephrotic syndrome. We therefore investigated the use of ACTH gel for nephrotic syndrome in the United States.

Patients and methods: Twenty-one patients with nephrotic syndrome treated with ACTH gel outside of research settings in the United States, with initiation of therapy by December 31, 2009, allowing a minimum 6 months follow-up. We defined complete remission as stable renal function with proteinuria falling to < 500 mg/day, and partial remission as stable renal function with > 50% reduction in proteinuria from 500 to 3500 mg/day.

Results: Twenty-one patients with nephrotic syndrome were treated: 11 with idiopathic membranous nephropathy (iMN), 4 with membranoproliferative glomerulonephritis (MPGN), 1 with focal segmental glomerulosclerosis (FSGS), 1 with minimal change disease (MCD), 1 with immunoglobulin A (IgA) nephropathy, 1 with class V systemic lupus erythematosus (SLE) glomerulonephritis, 1 with monoclonal diffuse proliferative glomerulonephritis, and 1 with unbiopsied nephrotic syndrome. ACTH was used as primary therapy for 3 patients; the remaining patients had previously failed a mean 2.3 immunosuppressive regimens. Eleven patients achieved a complete or partial remission, with 4 (19%) in complete remission. Of the 11 patients who achieved remission, 9 had iMN, 1 had FSGS, and 1 had IgA nephropathy. Of the 11 patients with iMN, 3 (27%) achieved complete remission and 6 (55%) achieved partial remission despite having previously failed a mean 2.4 therapies. Five patients reported steroid-like adverse effects, but there were no severe infections. The limitations were retrospective data analysis with short-term follow-up.

Conclusion: ACTH gel may be a viable treatment option for resistant nephrotic syndrome due to membranous nephropathy. Short-term data suggest that remission rates may approach 80%.

Keywords: nephrotic syndrome, membranous nephropathy, chronic kidney disease

Table 2 Dosing, duration, and outcomes of ACTH gel therapy for nephrotic syndrome

Patient	Diagnosis	ACTH gel dose (units)	Duration of ACTH therapy	Follow-up time	Pre-ACTH proteinuria (mg/day)	Last proteinuria (mg/day)	Outcome
1	iMN	80 SC twice weekly	6 months	8 months	4851	400	Complete remission
2	iMN	80 SC twice weekly	6 months	6 months	6749	1540	Partial remission
3	iMN	80 SC twice weekly	6 months	6 months	4598	1242	Partial remission
4	iMN	80 SC twice weekly	6 months	6 months	8153	1935	Partial remission
5	iMN	80 SC twice weekly	6 months	6 months	9000	3000	Partial remission
6	iMN	80 SC twice weekly	5 months	12 months	8900	6000	No response
7	iMN	40 SC twice weekly	12 months	14 months	3469	34	Complete remission
8	iMN	80 SC q 72 hrs	11 months	11 months	9150	2948	Partial remission
9	iMN	40 SC thrice weekly	6 months	7 months	11911	13,338	No response
10	iMN	40 SC thrice weekly	6 months	6 months	5700	694	Partial remission
11	iMN	80 SC twice weekly	12 months	13 months	2625	240	Complete remission
12	MPGN	80 SC twice weekly	4.5 months	8 months	13073	3741	No response[a]
13	MPGN	80 SC twice weekly	4 months	6 months	5500	4825	No response
14	MPGN	40 SC thrice weekly	6 months	6 months	12398	4560	Limited response
15	MPGN	80 SC twice weekly	6 months	6 months	10244	3878	No response[a]
16	MCD	80 SC twice weekly	4 months	8 months	18553	18,557	No response
17	FSGS	80 SC twice weekly	6 months	6 months	10275	2970	Partial remission
18	IgA nephropathy	40 SC q 72 hrs	8 months	8 months	4952	42	Complete remission
19	SLE class V	40 SC thrice weekly	5 months	8 months	1340	2290	No response[b]
20	Monoclonal DPGN	80 SC twice weekly	1 month	6 months	8560	8500	No response
21	NS	40 SC q 72 hrs	6 months	9 months	5805	8708	No response

Notes: [a]Drop in proteinuria occurred in the setting of significant (>25%) decline in eGFR, thus not meeting criteria for response to therapy; [b]While on ACTH gel therapy, proteinuria dropped from 1340 mg/day to 420 mg/day; after patient discontinued therapy due to concerns of weight gain, her proteinuria rebounded to 2290 mg/day.

Abbreviations: ACTH, adrenocorticotropin; DPGN, diffuse proliferative glomerulonephritis; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; iMN, idiopathic membranous nephropathy; MCD, minimal change disease; MPGN, membranoproliferative glomerulonephritis; NS, nephrotic syndrome without biopsy; SC, subcutaneous; SLE, systemic lupus erythematosus.

Table 1 Characteristics of patients in the United States treated with ACTH gel for nephrotic syndrome through December 31, 2009

Patient	Age	Gender	Race/ ethnicity	Diagnosis	Previous immunosuppression	eGFR (mL/min/1.73 m^2)	Proteinuria (mg/day)
1	59	Male	White	iMN	MMF, CNI	>60	4851
2	77	Male	Hispanic	iMN	MMF, CNI	21	6749
3	58	Male	White	iMN	Steroids + CTX, CNI, MMF	58	4598
4	55	Male	White	iMN	Steroids + CTX, CNI, MMF	57	8153
5	27	Male	White	iMN	Steroids, MMF, CNI	30	9000
6	24	Female	White	iMN	None	>60	8900
7	75	Female	White	iMN	Steroids + CTX	>60	3469
8	49	Male	White	iMN	Steroids, CNI	25	9150
9	46	Male	White	iMN	Steroids + CTX	20	11,911
10	53	Male	White	iMN	Steroids, Steroids + CTX	>60	5700
11	70	Female	White	iMN	Steroids, CNI, CTX	40	2625
12	81	Male	White	MPGN	Steroids, MMF, rituximab	25	13,073
13	28	Female	White	MPGN	Steroids, MMF, rituximab	23	5500
14	53	Female	White	MPGN	Steroids, MMF	11	12,398
15	47	Female	White	MPGN	MMF	21	10,244
16	57	Female	White	MCD	Steroids, MMF, CNI	15	18,553
17	63	Female	Hispanic	FSGS	Steroids, MMF, CNI	33	10275
18	75	Male	Black	IgA nephropathy	None	22	4952
19	32	Female	White	SLE class V	Steroids + MMF + CNI	>60	1340
20	36	Male	White	Monoclonal DPGN	Steroids, rituximab, MMF, CNI	19	8560
21	74	Male	White	NS[a]	None	12	5805

Notes: Conversion factor for eGFR: mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667; [a]Patient with nephrotic syndrome who did not undergo biopsy for specific diagnosis.

Abbreviations: CNI, calcineurin inhibitor; CTX, cyclophosphamide; DPGN, diffuse proliferative glomerulonephritis; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; iMN, idiopathic membranous nephropathy; MCD, minimal change disease; MMF, mycophenolate mofetil; MPGN, membranoproliferative glomerulonephritis; NS, nephrotic syndrome; SLE, systemic lupus erythematosus.

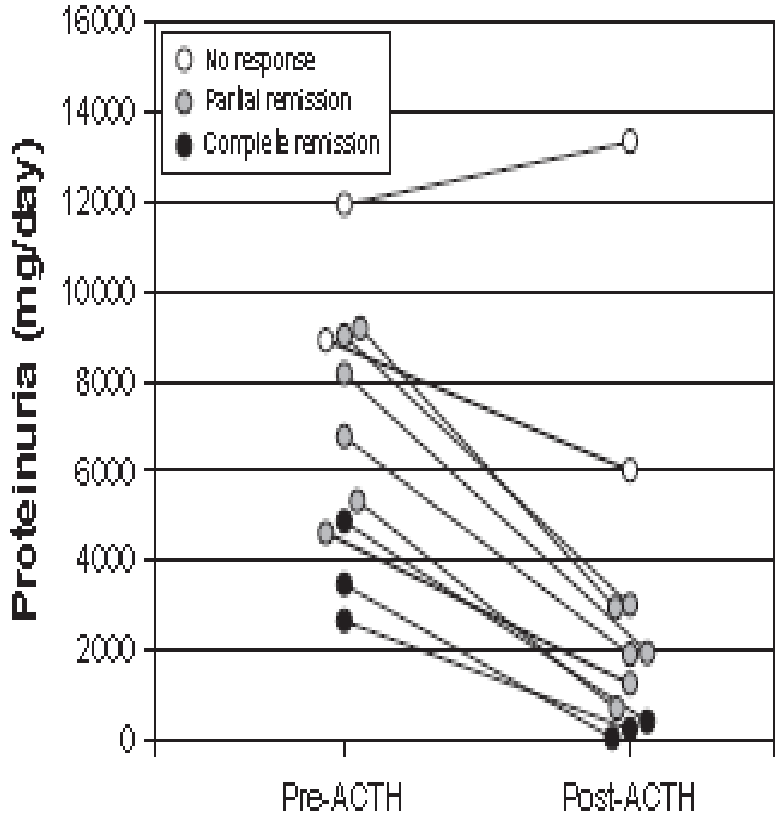

Figure 1 Changes in proteinuria with ACTH gel therapy in 11 patients with nephrotic syndrome due to membranous nephropathy.
Abbreviation: ACTH, adrenocorticotropin.

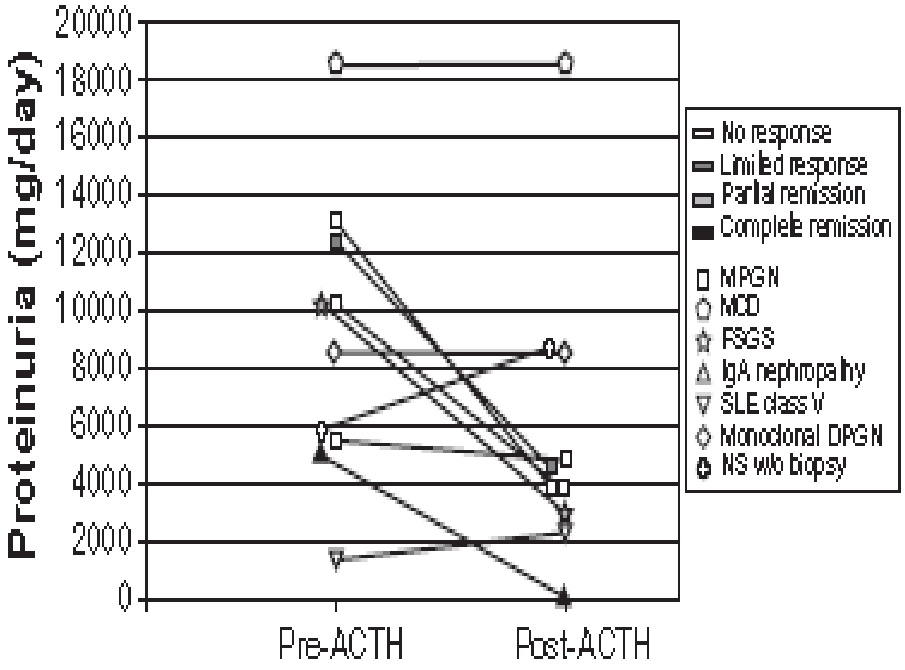

Figure 2 Changes in proteinuria with ACTH gel therapy in 10 patients with nephrotic syndrome due to etiologies other than membranous nephropathy.
Abbreviations: ACTH, adrenocorticotropin; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; MCD, minimal change disease; MPGN, membranoproliferative glomerulonephritis; NS, nephrotic syndrome without biopsy; SLE, systemic lupus erythematosus

The experience with ACTH, particularly in the United States, is far too preliminary to consider using this treatment outside of clinical research studies.


Thank You!